31. The injectable formulation of claim 21, wherein the concentration of the polymeric matrix comprising the biologically active agent is about 1 mg/mL to about 300 mg/mL of formulation.

32. The injectable formulation of claim 21, wherein the hyaluronic acid is selected from the group consisting of naturally occurring hyaluronic acid, an ester derivative of hyaluronic acid, an amide derivative of hyaluronic acid, a lactide derivative of hyaluronic acid, an acyl derivative of hyaluronic acid, a polyethylene glycol derivative of hyaluronic acid, a water-insoluble derivative of hyaluronic acid, and a salt of hyaluronic acid.

33. The injectable formulation of claim 21, wherein the hyaluronic acid is selected from the group consisting of N-acylurea modified hyaluronic acid and amino acid modified hyaluronic acid.

34. The injectable formulation of claim 21, wherein the hyaluronic acid is sodium hyaluronate.

SUPPORT FOR AMENDMENT

Claims 17 and 20 have been clarified. Claims 21-31 are supported by claims 4-16. Claims 32-34 are supported by the specification, page 4, line 21 through page 5, line 9, including the U.S. Patents incorporated by reference. Although the claims no longer refer to "hyaluronic acid or derivatives thereof," the term "hyaluronic acid" is defined in the specification as including various derivatives (page 5, line 1). Claims 32-34 are directed to some of these derivatives. No new matter has been added.

Attached herewith is a marked-up version of the changes made to the claims by this amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

REQUEST FOR RECONSIDERATION

Applicants would like to thank Examiners Kam and Low for the courteous and helpful discussion held with applicants' representatives on April 25, 2001. During this

discussion it was noted that the present invention includes a formulation comprising (a) hyaluronic acid, and (b) particles, the particles comprising a biologically active agent and a biocompatible polymeric matrix.

The formulation of a biologically active agent with a biodegradable polymer can provide for the sustained release of the agent into a patient. However, most of these formulations must be surgically implanted, or can be injected only through a needle having a large diameter. The formulation of biologically active agents with various liquids can provide for the administration of the agent through a needle of standard size, for example a 23-gauge needle or smaller. This can greatly improve patient compliance to the therapy. However, such formulations typically do not provide acceptable control over the rate with which the biologically active agent is released into the patient. The present invention overcomes these problems.

The present invention includes an injectable formulation, including hyaluronic acid and particles, the particles including a biologically active agent and a biocompatible polymeric matrix. This formulation provides for the administration of a biologically active agent by injection, as well as the controlled release of the biologically active agent into a patient.

The rejection of the claims under 35 U.S.C. §§ 102 and 103 over Igari et al. and Machida et al., alone or in combination, has been obviated by appropriate amendment. None of the applied references describe a formulation including hyaluronic acid and particles including a biologically active agent and a biocompatible polymeric matrix.

Machida et al. (EP 0263490 A2) describes a method of making a particulate formulation by mixing: (1) an organic phase comprising a biodegradable polymer and a biologically active agent and (2) an aqueous solution of hyaluronic acid (column 4, lines 14-34). Thus, hyaluronic acid is used as a medium for precipitating the particles containing the active agent. The particles produced by this method are administered by injecting a mixture of the particles with physiological saline (column 10, lines 22-29).

Igari et al. describes an injection vehicle for a biologically active agent comprising hyaluronic acid. The mixture of the biologically active agent and injection vehicle can be combined with a solution containing a biodegradable polymer (column 15, lines 35-49).

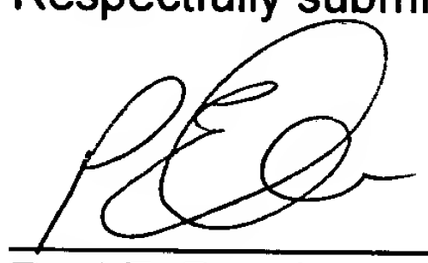
This combination may then be used to administer the agent, or the mixture can be converted into microspheres. The mixture of active agent and injection vehicle can also be lyophilized into a powder and then dissolved in another injection vehicle, such as water or physiological saline (column 8, lines 48-63).

The present invention includes an injectable formulation, including hyaluronic acid and particles, the particles including a biologically active agent and a biocompatible polymeric matrix. Machida et al. describes a method of making particles; no particles containing a biodegradable polymer and a biologically active agent are described. Igari et al. describes a solution containing a biodegradable polymer, but not particles. In addition, there is no suggestion in these references of a formulation including hyaluronic acid, and particles containing a biologically active agent and a biocompatible polymeric matrix. Accordingly, applicants submit that the claimed invention is neither anticipated by, nor obvious over, the applied references. Withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. § 112 has been obviated by appropriate amendment.

Applicants submit that the application is in condition for allowance. Early notice is respectfully requested.

Respectfully submitted,



Paul E. Rauch, Ph.D.
Registration No. 38,591
Attorney for Applicant

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, ILLINOIS 60610
(312) 321-4200

VERSION WITH MARKINGS TO SHOW CHANGES MADE

17. (Amended) [A pharmaceutical] An injectable formulation, comprising:

(a) particles comprising a biocompatible polymeric matrix, the polymeric matrix comprising a poly(lactide-co-glycolide) [polymer];

(b) [an effective amount of] a biologically active polypeptide dispersed within the polymeric matrix; and

(c) an injection vehicle comprising hyaluronic acid [or a derivative thereof].

20. (Amended) A method for administering a [pharmaceutical formulation of Claim 17] biologically active agent, comprising:

injecting the composition of claim 17 into a patient in need thereof [the pharmaceutical formulation] through a 23-gauge or smaller needle.